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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,037	02/22/2000	DAVID MICHAEL HEERY	ASZD-P01-228	6259

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EXAMINER	
DUNSTON, JENNIFER ANN	
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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/423,037	HEERY ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-22* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 14-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/2007 has been entered.

Receipt is acknowledged of an amendment, filed 10/1/2007, in which claim 1 was amended. Currently, claims 1 and 3-22 are pending in the instant application.

Any rejection of record in the previous office actions not addressed herein is withdrawn.

Election/Restrictions

Applicant elected Group I, LXXLL, SRC-1 and oestrogen receptor species without traverse in the reply filed 11/13/2001.

Claims 14-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/13/2001.

Claims 5-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/13/2001.

Currently, claims 1, 3, 4 and 7-13 are under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le Douarin et al (The EMBO Journal, Vol. 15, No. 23, pages 6701-6715, 1996, cited as reference VR on the IDS filed 2/23/2000; see the entire reference) in view of Scanlan et al (US Patent No. 6,236,946 B1; see the entire reference). This is a new rejection.

Le Douarin et al teach that nuclear receptors (NR) contain a region known as the AF-2 activating domain (AD) core, which is highly conserved and present in all known transcriptionally active members of the NR superfamily (e.g., page 6701, paragraph bridging columns). Several proteins interact with the AF-2-containing ligand binding domain (LBD) of several NRs (steroid, thyroid, vitamin D3 and retinoid receptors) in the presence of agonistic ligands but not in the presence of antagonists; these interacting proteins include RIP140, TIF1,

Trip/SUG1, SRC-1/p160, CBP and TIF2/Grip1 (e.g., paragraph bridging pages 6701-6702). Le Douarin et al teach the fusion of various TIF1 mutants to the ER DBD to map the regions required for interaction with retinoid X receptor (RXR) (e.g., pages 6701-6705, NRs and the mouse HP1 homologues interact with two adjacent but distinct domains of TIF1). Le Douarin et al identify a minimal RXR-interacting domain in TIF1, which mapped between residues 723 and 735 of TIF1 (e.g., page 6705, left column, 1st paragraph; Figure 3). The 10 amino acid sequence LLTSLLLNSS was shown to specifically interact with RXR, whereas mutation to LLTSELLNSS or LLTSAALNSS abolished the interaction (e.g., page 6705, left column, 1st paragraph; Figure 3A). This interaction requires the AF-2 region of RXR (e.g., page 6705, left column, 1st paragraph; Figure 3). Le Douarin et al conclude that TIF1 contains a 10 amino acid long sequence that is sufficient on its own to functionally interact with NRs in both a ligand- and AF-2-dependent manner, and similar sequences are present in RIP140 and TRIP3 (e.g., page 6705, left column, 1st paragraph). Le Douarin et al demonstrate that the conserved 10 amino acid sequence, referred to as an NR box, is sufficient to interact with RAR and ER, whether the NR box is obtained from TIF1 or RIP140 (e.g., Figure 3B). The NR and NR box interactions were tested by Le Douarin et al in the context of a yeast two-hybrid assay, where a first component, which is the 10 amino acid NR box fragment of a nuclear protein is operably linked to a ER-DBD, and where a second component comprising a liganded nuclear receptor transcription factor or fragment thereof, where the fragment comprising the LBD and AF-2 region, is operably linked to a VP16 activation domain, and where the presence or absence of an interaction between the first and second component is detected by the expression of OMPdecase activity (e.g., page 6713, Transactivation Assays; Figure 3).

Le Douarin et al do not teach the addition of a potential inhibitor compound to the interaction assay to identify a compound that is capable of inhibiting the interaction between the NR box (containing an LXXLL motif) and the nuclear receptor protein, or fragment thereof.

Scanlan et al teach methods for the generation of nuclear receptor synthetic ligands based on the three dimensional structure of nuclear receptors, where the ligand preferably contains an extension moiety that coordinates AF-2 of the nuclear receptor (e.g., Abstract; column 6, line 32 to column 7, line 15). Scanlan et al teach that the computation methods can be used to design drugs for a variety of nuclear receptors, including retinoid (RX) receptors and estrogen receptors (ERs) (e.g., column 4, lines 49-55). Scanlan et al teach that once a computationally designed ligand is synthesized, it can be tested using assays to establish its activity as an agonist, partial agonist or antagonist (e.g., column 7, lines 3-7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the two-hybrid interaction method of Le Douarin et al to include the computationally designed ligand taught by Scanlan et al because Le Douarin et al teach it is within the ordinary skill in the art to use the two-hybrid assay to demonstrate the presence or absence of an interaction between an NR box (containing an LXXLL motif) and a nuclear receptor such as an RXR receptor or an estrogen receptor, and Scanlan et al teach computational design of ligands that bind to the AF-2 region that is necessary for interaction with the NR box.

One would have been motivated to make such a modification in order to receive the expected benefit of determining whether the computationally designed ligand functions as an inhibitor of NR box/AF-2 interaction (nuclear protein/nuclear receptor interaction). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent

any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 3, 4, 7 and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le Douarin et al (The EMBO Journal, Vol. 15, No. 23, pages 6701-6715, 1996, cited as reference VR on the IDS filed 2/23/2000; see the entire reference) in view of Dedhar (US Patent No. 5,854,202; see the entire reference). This is a new rejection.

Le Douarin et al teach that nuclear receptors (NR) contain a region known as the AF-2 activating domain (AD) core, which is highly conserved and present in all known transcriptionally active members of the NR superfamily (e.g., page 6701, paragraph bridging columns). Several proteins interact with the AF-2-containing ligand binding domain (LBD) of several NRs (steroid, thyroid, vitamin D3 and retinoid receptors) in the presence of agonistic ligands but not in the presence of antagonists; these interacting proteins include RIP140, TIF1, Trip/SUG1, SRC-1/p160, CBP and TIF2/Grip1 (e.g., paragraph bridging pages 6701-6702). Le Douarin et al teach the fusion of various TIF1 mutants to the ER DBD to map the regions required for interaction with retinoid X receptor (RXR) (e.g., pages 6701-6705, NRs and the mouse HP1 homologues interact with two adjacent but distinct domains of TIF1). Le Douarin et al identify a minimal RXR-interacting domain in TIF1, which mapped between residues 723 and 735 of TIF1 (e.g., page 6705, left column, 1st paragraph; Figure 3). The 10 amino acid sequence LLTSLLLNSS was shown to specifically interact with RXR, whereas mutation to LLTSELLNSS or LLTSAALNSS abolished the interaction (e.g., page 6705, left column, 1st paragraph; Figure 3A). This interaction requires the AF-2 region of RXR (e.g., page 6705, left

column, 1st paragraph; Figure 3). Le Douarin et al conclude that TIF1 contains a 10 amino acid long sequence that is sufficient on its own to functionally interact with NRs in both a ligand- and AF-2-dependent manner, and similar sequences are present in RIP140 and TRIP3 (e.g., page 6705, left column, 1st paragraph). Le Douarin et al demonstrate that the conserved 10 amino acid sequence, referred to as an NR box, is sufficient to interact with RAR and ER, whether the NR box is obtained from TIF1 or RIP140 (e.g., Figure 3B). The NR and NR box interactions were tested by Le Douarin et al in the context of a yeast two-hybrid assay, where a first component, which is the 10 amino acid NR box fragment of a nuclear protein is operably linked to a ER-DBD, and where a second component comprising a liganded nuclear receptor transcription factor or fragment thereof, where the fragment comprising the LBD and AF-2 region, is operably linked to a VP16 activation domain, and where the presence or absence of an interaction between the first and second component is detected by the expression of OMPdecase activity (e.g., page 6713, Transactivation Assays; Figure 3).

Le Douarin et al do not teach the addition of a potential inhibitor compound to the interaction assay to identify a compound that is capable of inhibiting the interaction between the NR box (containing an LXXLL motif) and the nuclear receptor protein, or fragment thereof. Le Douarin et al do not teach the method where the potential inhibitor compound is a member of a peptide library based upon the NR box (containing the LXXLL signature motif).

Dedhar teaches that it is desirable to identify peptides that modulate the activity of hormone receptors, including estrogen receptor (e.g., column 1, lines 7-53). Dedhar et al teach that it is important to identify proteins that interact with hormone receptors, determine if they inhibit or promote hormone receptor induced gene transcription (e.g., column 2, lines 1-15).

Once such interacting proteins are identified, Dedhar teaches that one should manipulate proteins to further inhibit or promote hormone receptor induced gene transcription, for example, by using peptides that bind to such proteins or their mimetics (e.g., column 2, lines 1-24). Dedhar et al teach a collection of peptides based upon a sequence present in all hormone receptors that is responsible for interaction with calreticulin (e.g., Tables II-IV). Dedhar et al teach methods of assaying the peptides to modulate calreticulin activity *in vitro* and *in vivo* (e.g., Examples 6-7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the interaction assay of Le Douarin et al to include the administration of peptides based upon the NR box sequence and test for inhibition of NR box-nuclear receptor interaction, because Le Douarin et al teach it is within the ordinary skill in the art to use the two-hybrid assay to test for an interaction between the NR box of a nuclear protein and a nuclear hormone receptor and Dedhar teaches that it is important to identify modulators of nuclear hormone-protein interactions. Dedhar specifically teaches the identification of a conserved binding sequence and the use of the sequence to synthesize a library of peptides that are tested for modulation of nuclear hormone receptor-protein interaction. Thus, it would have been obvious to apply the techniques of Dedhar to the NR box-nuclear hormone receptor interaction taught by Le Douarin.

One would have been motivated to make such a modification in order to receive the expected benefit of identifying peptide modulators of nuclear hormone receptor-protein interaction as taught by Dedhar. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Le Douarin et al (The EMBO Journal, Vol. 15, No. 23, pages 6701-6715, 1996, cited as reference VR on the IDS filed 2/23/2000; see the entire reference) in view of Dedhar (US Patent No. 5,854,202; see the entire reference) as applied to claims 1, 3, 4, 7 and 9-13 above, and further in view of Collingswood et al (PNAS, USA, Vol. 94, pages 248-253, January 1997; see the entire reference) and Spencer et al (GenBank Accession No. U90661.1, GI: 1906027, March 25, 1997; see the entire reference). This is a new rejection.

The teachings of Le Douarin et al and Dedhar are described above and applied as before. Further, Le Douarin et al teach that the conserved residues of the NR box are LxxLLL (e.g., Figure 3D).

Le Douarin et al and Dedhar et al do not teach the method where the 10 amino acid fragment of a nuclear protein comprises the signature motif LxxLL and is from SRC-1.

Collingswood et al teach that thyroid hormone receptor (TR) contains an AF-2 domain that is conserved among nuclear receptors (e.g., page 248, right column, 1st full paragraph). Collingswood et al teach that RIP140 exhibits strong hormone-dependent interaction with TR and estrogen receptor, as does SRC-1 (e.g., page 250, Location of Homologous Leucine in Structure of the rTRα Ligand-Binding Domain and Protein-Protein Interaction Assays; Figure 4).

Spencer et al teach that human steroid receptor coactivator-1 mRNA encodes a protein that contains a 10 amino acid sequence that is the following: **SLGPLLLEAL** (e.g., line 3 of the protein sequence).

Le Douarin et al teach that the NR box is responsible for nuclear hormone receptor (e.g., estrogen receptor) interaction by TIF1 and RIP140 and is a ten amino acid sequence that contains the conserved sequence **LxxLLL**. Collingswood et al teach that SRC-1 interacts with estrogen receptor and thyroid hormone receptor as does RIP140. Spencer et al teach the presence of the NR box of Le Douarin et al in the SRC-1 sequence. Because SRC-1 contains the NR box of Le Douarin et al and is capable of interacting with estrogen receptor and thyroid hormone receptor, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the NR box of SRC-1 in the method of Le Douarin et al and Dedhar in order to achieve the predictable result of identifying inhibitors of SRC-1/hormone receptor interaction based upon the presence of an NR box.

Response to Arguments - 35 USC § 103

The rejection of claims 1, 7, 9 and 12 under 35 U.S.C. 103(a) as being unpatentable over Lee et al in view of Onate et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/1/2007.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Daniel M. Sullivan/
Primary Examiner
Art Unit 1636